Commentary

Reduced Risk Cigarettes: An Essential Component of Risk Reduction Strategy

Introduction

Recent publications have challenged the merits of lower-risk cigarettes and questioned whether the public should have access to them (1,2). Although this debate has been ongoing for many years, participation remains largely limited to representatives of the anti-smoking community and the tobacco industry. To date, participation by the general scientific community has been minimal.

The debate over lower-risk cigarettes is fueled by the fact that many members of the public health community advocate smoking avoidance and cessation as the only acceptable ways to reduce the risks associated with smoking. Given that approximately 50 million American adults currently smoke and that tens of millions will, without doubt, continue to do so in the years ahead, the utility of this approach as the sole risk reduction strategy is questionable. There are, however, others who advocate a three-pronged risk-reduction approach that focuses on discouraging those who don't use tobacco products from starting to use them, encouraging smokers and other tobacco users to quit, and reducing the inherent risks associated with the tobacco products themselves.

Scientists from a number of disciplines have opined that efforts should be directed to reduce the risks inherent in the tobacco products themselves (3,4,5). Despite this interest in the development of reduced risk cigarettes, to date, few opportunities have been created in the United States that facilitate discussion of what constitutes reduced risks. We believe it is essential to develop a forum for constructive discussion and establishment of a framework in which cigarettes that have the potential to reduce health risks can be evaluated.

To this end, we agree with Holzman (1) that "the best should not be the enemy of the good." However, that is exactly what will occur unless those of us involved in the effort to reduce the risks of cigarettes -- manufacturers, scientists and public health officials -- take a rational approach to product modification.

History of Reduced Risk Tobacco Products

R. J. Reynolds Tobacco Company (RJRT) has for decades actively pursued the development of cigarettes with the potential to reduce the risks associated with smoking. RJR's efforts to develop cigarettes with the potential to reduce risks have been guided by a simple, intuitive approach: *Less ought to be better.* That is, reductions in tobacco smoke constituents should result in reductions in the risks associated with the use of cigarettes and other tobacco products. As indicated below, this intuitive approach has also been the cornerstone of recommendations made by the scientific community and governments for approximately 30 years.

During the 1960s and 1970s, the federal government sponsored a number of initiatives to investigate the feasibility of developing "safer cigarettes" (6). Cigarette manufacturers were invited to, and did, participate in these efforts. These efforts generally concluded that general and specific reductions in the yields of smoke constituents represented a viable approach to reducing the risks of tobacco products (7,8). The 1981 Surgeon General's Report suggested that: "...smokers who are unwilling or as yet unable to quit are well advised to switch to cigarettes yielding less 'tar' and nicotine, provided they do not increase their smoking or change their smoking in other ways." That report also recommended efforts that "could lead to the selective removal of toxic substances from smoke."

During the past several decades, cigarette design innovations have focused largely on "tar" and nicotine reductions using techniques and tools such as reconstituted tobacco, expanded tobacco, more porous cigarette papers, filtration, and filter ventilation. As a result of these efforts, average "tar" and nicotine yields of U.S. cigarettes have been reduced by more than 60% during the past 40 years (9). Today, more than half of all smokers in the United States choose products with U.S. Federal Trade Commission (FTC) yields below 12 mg "tar" and 0.9 mg nicotine. However, efforts to produce additional reductions in total "tar" yields while maintaining consumer product acceptability seem to have reached the point of diminishing returns. The sales-weighted "tar" and nicotine average, which had been declining for three decades, leveled off in the early 1980's. Less than 5 percent of smokers find the lowest-"tar" category of cigarettes acceptable. In addition, smokers of filtered cigarettes adjust their smoking behavior to obtain yields of smoke constituents that can be higher or lower than the machine yields of these products. These changes in smoking behavior, which are often referred to as compensation, make it difficult to further reduce actual exposure to "tar" using conventional techniques (10,11).

RJRT and other companies have attempted to develop alternative cigarette designs that can provide additional reductions not achievable with the design techniques that have traditionally been used for cigarettes. By example, Premier, a cigarette that RJRT test marketed in 1988-89, heated, rather than burned, tobacco. Because of its unique design, many of the compounds commonly found in cigarette smoke were dramatically reduced in (or eliminated from) its smoke. In addition, a comprehensive battery of toxicological tests indicated that the smoke from Premier had significantly reduced biological activity compared to that from tobacco-burning cigarettes (12,13,14). Premier failed in the marketplace because its taste and aroma were unacceptable and because it was denounced by federal agencies and public health groups, who perceived Premier as a direct threat to their stated goal of achieving a smoke-free society.

In 1996, following several additional years of intense development efforts, Reynolds Tobacco began to test market a prototype of Eclipse, a new cigarette that was based on the same concept as Premier – heating tobacco. Although Eclipse is much more acceptable to smokers than Premier, Eclipse has not achieved commercial success. We believe this is due in part to Eclipse's inherent differences from other cigarettes. RJRT believes that, if the risk reduction potential of Eclipse could be communicated to smokers, they would be more likely to overcome product differences (15).

Measuring Progress

Perhaps the most difficult aspect of developing cigarettes with the potential to reduce the risks associated with smoking is determining how to measure progress toward that goal. Despite decades of debate, the scientific community has failed to develop consensus regarding what cigarette modifications might lead to reductions in risk and how those reductions should be measured and characterized.

Those who would require long-term epidemiological studies before acknowledging that a cigarette might have the potential to reduce risk are essentially arguing for a 20- to 30-year evaluation of a design modification prior to introduction and communication of the potential benefits. Preventing the introduction of such products until evidence of this type is available represents a poor public health choice because it would effectively stifle (rather than promote) the development of new cigarettes – a result that is inconsistent with the goal of risk reduction. Efforts should be made to reach a consensus on logical and practical standards that must be met to allow the marketing (with appropriate claims) of potentially reduced risk products.

As part of ongoing stewardship efforts, RJRT has developed a tiered testing strategy to evaluate the potential for new ingredients, tobacco processes, and technological developments to increase or reduce the biological activity that results from burning tobacco. The U.S. Food and Drug Administration (U.S. FDA) introduced the concept of tiered testing requirements in 1982 (16). Tiered testing strategies have been emp ed by U.S. regulatory agencies to evaluate direct food additives and color additives in ood for approximately twenty years (17). As applied by the U.S. FDA, this concept is based on the assumption that the degree of effort expended to reduce the uncertainty about the safety of an additive should relate in some logical way to the actual likelihood that the additive poses a health risk to the public. Similarly, the tiered testing strategy developed by RJRT was created to provide a conceptual framework based on level of concern to facilitate the design of toxicological evaluation programs.

Within the context of this framework, decisions regarding the design of a toxicological evaluation program are determined by considering two factors – the level of human exposure and the potential for toxicity. The level of human exposure reflects not only the level (frequency and magnitude) of expected exposure but also the intended use level in the cigarette. The potential for toxicity is determined based upon available information (structure activity relationships, *in vitro* data, *in vivo* data). All data, including positive and negative findings, are considered to derive a weight-of-the-evidence conclusion. Combined, these factors, in conjunction with scientific judgment, provide a means to assess the appropriate level of concern. In brief, the level of concern is a relative measure of the extent to which a product modification may present a potential risk or a potential to present a reduced risk.

Based upon the level of concern, an appropriate evaluation program (pre-clinical and/or clinical) is designed. For example, a modification determined to represent a low level of concern (such as a subtle change in the formulation of a cigarette paper) might require no significant toxicological evaluation. By contrast, a modification determined to represent a high level of concern, such as the introduction of novel technology exemplified by Premier and Eclipse, would require more extensive scientific evaluation. The concern level attributed to these cigarettes is a direct reflection of the uniqueness of the technology employed as well as the significant potential to reduce cigarette smoke toxicity. Such an evaluation would include an examination of a number of smoke constituents (which have been identified by the Surgeon General and others to have the potential to contribute to the risks associated with smoking) as well as both *in vitro* and *in vivo* toxicology.

At RJRT, comparative studies typically constitute the foundation of the toxicological evaluation programs designed to address the potential of new technology to reduce the biological activity associated with burning tobacco. In general, the comparative approach is based on a benchmark established using data generated on either a reference cigarette (such as one or more of the University of Kentucky reference cigarettes) or a survey of the marketplace. Market survey data are generated by obtaining and evaluating a representative sample of the cigarette brands in commerce (18,19).

The utility of the Kentucky reference cigarettes as representative benchmarks of the cigarette market has been previously described (18,19). Therefore, it is appropriate to use these reference cigarettes as a benchmark in comparative studies designed to characterize the potential of new technologies to reduce the biological activity associated with burning tobacco.

Market survey data provide a useful tool to extend the conclusions drawn in the direct head-to-head comparative studies to the broader context of the marketplace. Prior studies of smoke composition (constituent yield) and associated toxicity (Ames activity) have demonstrated that current cigarettes are generally similar. Constituent yields and Ames activity are in general predicted by 'tar' yield. These data indicate that differences in product (exemplified by the diversity of the marketplace) generally do not alter either composition of cigarette smoke or the activity of cigarette smoke condensate on a specific activity basis.

Therefore, it is unnecessary to completely characterize the marketplace on a by-brand basis in order to soundly demonstrate the risk-reduction potential of new technology. The potential of new technology to reduce the biological activity associated with burning tobacco may be effectively evaluated in terms of the existing cigarette brands through the use of market benchmarks. Taken as a whole, this approach can be effectively employed on a weight-of-the-evidence basis to measure progress toward reducing the biological activity associated with burning tobacco.

A comparative approach for measuring progress with cigarettes that have the potential to reduce risk against cigarettes currently on the market has been referred to as the Rule of First Approximation. It has been suggested that, rather than waiting for the results of prospective long-term clinical trials, surrogate measures could be employed to make a judgment regarding the risk reduction potential of a cigarette. As envisioned, such an approximation would facilitate the more rapid entry of potential reduced risk cigarettes into the marketplace (20,21).

Therefore, the comparative approach would not require a series of long-term clinical trials similar to the testing required by the U.S. FDA to make therapeutic drug claims. The comparative approach would rely on the weight of the evidence from chemistry and toxicology compared to a suitable benchmark of marketed cigarettes to justify short-term clinical tests that rely on surrogate markers. If progress can be demonstrated

using this comparative approach, then appropriate claims about the potential for risk reduction would be permitted. This approach would permit a more rapid introduction of modified cigarettes into the market and realization of the benefit of reduced risk products.

Cigarette design and performance is a complicated, interlocking web of factors and parameters. Due to the fact that smoking is a complicated behavior, viewing any of these parameters in isolation ignores the potential effects that individual changes have on other parameters or on the overall performance of the complex system. For example, design changes that result in "tar" reductions might not result in corresponding vapor-phase reductions. Limiting nicotine yields or removing nicotine from tobacco could actually increase potential health risks by prompting some smokers to smoke more cigarettes, or to smoke more intensely, and, therefore, increase exposure to "tar" (22,23,24,25). Design changes that potentially reduce some risks may not reduce, or may theoretically increase, other risks associated with smoking.

Given the complexity of the problem, a weight-of-the evidence approach must be adopted to determine whether new cigarettes and cigarette designs might have the potential to reduce the risks associated with smoking. Further, it is unlikely that a new cigarette design or individual design change will completely address all areas of potential risk. Therefore, it would be unreasonable, and counterproductive, to judge potential improvements against a standard that requires the reduction of all potential risks.

Communicating with Smokers

Regardless of how much progress can be made in developing tobacco products that potentially reduce risks, those products will not have any positive public health impact unless smokers are willing to try them and switch to them. Our experience with Premier, Eclipse and other cigarettes demonstrates that smokers are unwilling to make significant trade-offs in taste, ritual or other factors in the absence of significant incentive to do so.

The ability to provide consumers with information regarding potential benefits associated with new products that have the potential to reduce risk is essential if design modification as a risk reduction strategy is to succeed. Until the government and the scientific and public health communities can reach consensus on these issues and clearly communicate that position to the public, we believe that little, if any, additional progress will be made in marketing of consumer-acceptable tobacco products that have the potential to reduce the risks associated with smoking.

Discussion

Based on learning obtained from a long history of efforts, the following approaches offer the greatest opportunity for developing cigarettes that have the potential to reduce the risks associated with smoking and that will be accepted by smokers:

1. Continuing to pursue general and specific smoke constituent reductions in tobacco-burning cigarettes.
2. Continuing to develop and refine alternative cigarette designs (such as heating tobacco) that offer substantial general reductions not achievable through design techniques traditionally used for cigarettes.
3. Finding ways to alter "tar"/nicotine ratios, to achieve additional general "tar" reductions.

A regulatory framework that encourages the development of cigarettes with the potential to reduce the risks associated with smoking, and the dissemination of appropriate information about such cigarettes, as well as other choices for smokers would facilitate development efforts. This framework should encourage the development and use of such cigarettes while preserving smokers' freedom to choose from the full range of tobacco products required to meet consumer demands, for the following reasons:

1. Should restrictions be put in place to limit consumer options, many smokers might simply take steps to defeat those limitations. For example, faced with limits in total cigarette yields, some smokers may smoke more cigarettes, smoke their cigarettes more intensely, modify their cigarettes to defeat the reductions (e.g., tearing the filters off) or seek more acceptable products from other sources (black-market products produced in other countries).

2. A wide range of products preserves the rights of adult smokers to exercise their freedom to choose the tobacco products they deem to be most acceptable in terms of taste, pleasure and quality.

In recent years, many previous advocates of lower-yield cigarettes have abandoned their support for these efforts, and many anti-smokers and plaintiffs' lawyers have criticized the very tools and techniques manufacturers have used to achieve dramatic reductions in "tar" and nicotine. Many now take the position that prevention and cessation are the only acceptable approaches to reduce risks from tobacco use. As support for this opposition, they contend that lower-yield products lead smokers to change their smoking behavior and "compensate" for the lower yields. However, the available data demonstrate that not all smokers compensate, and, even among those who do, many do not compensate completely, or do so only for a short period of time after switching to lower-yield cigarettes (10,26,27).

Some members of the public health community have been openly hostile to any tobacco product that could be perceived as reducing risks, because it has been hypothesized that the presence of such a product could discourage smokers from quitting (4). In the absence of empirical data, it is unknown if a cigarette like Eclipse will influence quit rates. Even if quit rates are impacted, additional labeling may be employed to reinforce the fact that the best way to reduce the risks from smoking is, in fact, to quit. Further, for adults who continue to smoke, a cigarette like Eclipse clearly represents a viable option. It is essential that public health policy should include a renewed focus on reducing the risk of cigarettes and other tobacco products, and that such efforts should be encouraged rather than attacked.

Although these issues have yet to be addressed in the United States, RJRT has been participating in a process sponsored by Health Canada (28,29) to grapple with how to facilitate the introduction of innovative tobacco products that have the potential to reduce risk. It is time that we all work together and directly address the issues discussed herein. Working together, we can create a framework where cigarettes that have the potential to reduce risks can be developed, evaluated and made available to those Americans who choose to smoke.

For progress to occur, public health scientists must be more objective in evaluating the efforts of cigarette manufacturers to create new types of cigarettes that have the potential to reduce the risks associated with cigarette smoking.

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